Fundamental Aspects of Hypogonadism in the Aging Male

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With aging in men, serum testosterone levels decline progressively and the prevalence of hypogonadism increases; these changes are associated with alterations in androgen-regulated physiological functions. In young hypogonadal men, similar alterations improve with testosterone replacement. In older men, short-term testosterone treatment trials suggest benefits (eg, on body composition and bone mineral density), without significant adverse effects. Therefore, androgen deficiency may contribute to physiological decline with aging, and testosterone therapy is reasonable for older men with clinical manifestations of androgen deficiency and low testosterone levels. However, the long-term benefits and potential risks (eg, for prostate disease) of testosterone treatment in older men are unknown.

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In men, serum testosterone concentrations decline progressively with aging, such that an increasing proportion of older men have testosterone levels below the normal range for young men (ie, in the hypogonadal range).[1–3] This decline in testosterone occurs concurrently with a number of age-associated changes in androgen-regulated physiological functions, including alterations in body composition, decreased energy and muscle strength, reduced sexual desire and function, changes in well-being and mood, and diminished cognitive function.[4] Similar changes occur in young hypogonadal men, and testosterone replacement therapy improves function in these men. Therefore, it is hypothesized that low serum

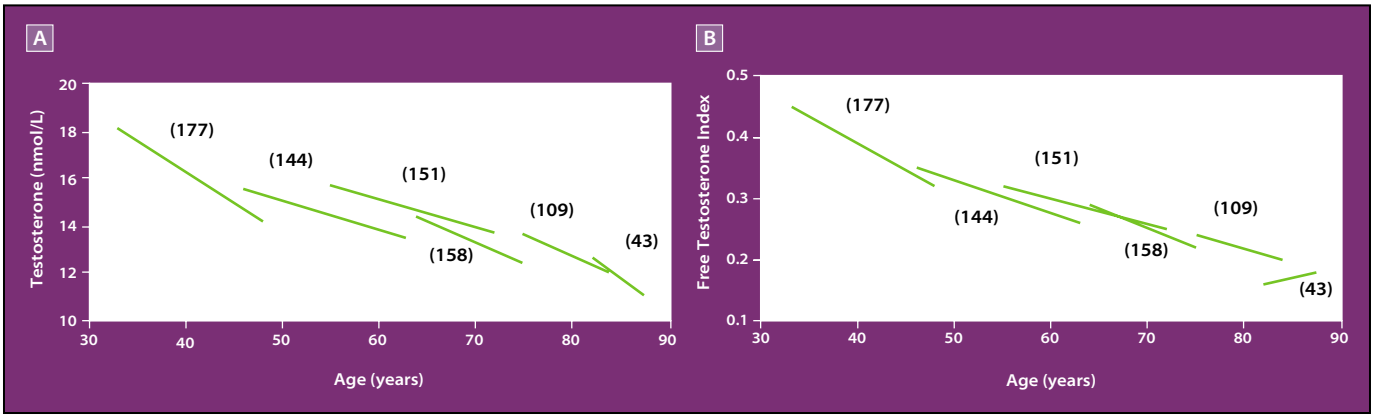

Figure 1. *Longitudinal decline in* (A) *serum total testosterone and* (B) *free testosterone index (total testosterone/sex hormone-binding globulin) with aging in men. Each line has a slope equal to the mean of longitudinal slopes in each decade, and is centered on the median age for men in each cohort (number in parentheses) from the fourth to tenth decade. Adapted with permission from Harman et al.*[2]

testosterone concentrations may play a role in age-related physiological decline and that testosterone treatment for older men with low testosterone levels may also improve function.

The physiological and clinical significance of the aging-related decline in serum testosterone levels in men is unclear, particularly because testosterone concentrations in some older men may remain within the broad normal range for young men. At present, there is insufficient evidence to support the notion that a decline in serum testosterone levels within the normal range is associated with significant alterations in physiological function. So clinically, it is most appropriate to define hypogonadism in the aging male, the so-called "andropause," as a decline in serum testosterone in older men to levels below the normal range for young men, with associated clinical manifestations consistent with androgen deficiency. Therefore, the definition of hypogonadism is the same for all men, irrespective of age. In contrast to hypogonadism in young men, however, androgen deficiency in older men is usually less severe and more difficult to diagnose using conventional serum testosterone assays. Furthermore, the manifestations of androgen deficiency are often subtle and may be attributable to multiple other etiologic factors (ie, the manifestations are nonspecific). The decline in testosterone concentrations is a consequence both of aging of the reproductive axis per se, and age-associated co-morbid illness and use of certain medications. Regardless of the etiology, however, androgen deficiency may contribute, at least in part, to age-related decrements in physiological function and cause clinical manifestations.

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In addition to the term *andropause*, hypogonadism in the aging male has also been referred to as *androgen-deficiency in the aging male (ADAM)* or *partial androgen deficiency in the aging male (PADAM)*. Regardless of whether these terms were intended to do so, they have been interpreted as defining a unique syndrome in older men and have created controversy and confusion on the part of practicing clinicians and the lay public. Therefore, from a clinical standpoint, it is better to use the term *male hypogonadism* for individuals with manifestations of androgen deficiency and low serum testosterone levels, irrespective of age, and to consider the complexities of this diagnosis and its treatment in the aging male.

Age-Related Decline in Serum Testosterone Levels

In men, aging is associated with a gradual and progressive decline in serum total testosterone levels at a rate of approximately 1% per year after age 30 years (Figure 1).[1–3]

Approximately 20% of men in their 60s and approximately 50% of men in their 80s have serum total testosterone levels significantly below those of young men (Figure 2).[2] Furthermore, compared with healthy older men, men who have co-morbid illnesses (eg, chronic renal, liver, or pulmonary disease, malignancy), take certain medications (eg, glucocorticoids and central nervous system–active medications), or are malnourished have lower serum testosterone concentrations.[5] Therefore, compared with healthy aging males, sick older men have a higher prevalence of testosterone levels below the normal range for young men.[6]

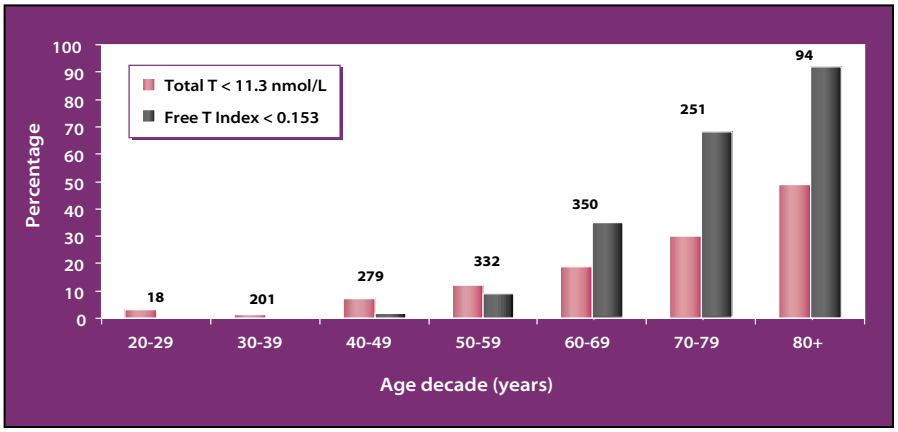

Figure 2. *The prevalence of hypogonadism in the aging male. Each bar indicates the percentage of men in each decade with total testosterone (T) < 11.3 nmol/L (325 ng/dL) (gray bars) or free testosterone index (total T/sex hormone-binding globulin) < 0.153 (black bars), both < 2.5th percentile. Numbers over each pair of bars represent the number of men studied in each decade. Adapted with permission from Harman et al.*[2]

Approximately 98% of circulating testosterone is bound to serum proteins, predominantly sex hormone-binding globulin (SHBG) and albumin, so that only 1%–2% of testosterone is free in circulation.[7] Testosterone is bound tightly to SHBG, so that SHBG-bound testosterone is not available to most tissues for biological action. In contrast, testosterone is bound weakly to albumin, so that both albumin-bound and free testosterone are bioavailable to most target tissues for action. Because SHBG concentrations increase with aging, serum free and bioavailable (free plus albumin-bound) testosterone concentrations decline at a greater rate (~2%–3% per year) than total testosterone levels with aging, and a larger percentage of older men have free and bioavailable testosterone levels below those of young men (Figure 2).[1–3]

In the laboratory evaluation of male hypogonadism, it is important to be aware that serum total testosterone assays measure both free testosterone and testosterone bound to SHBG and albumin, and common clinical situations that alter SHBG affect total testosterone measurements in the same direction.[5] It is also important to appreciate that free testosterone measurements using direct solid-phase analog methods (used by most local laboratories) also vary directly with alterations in SHBG levels and therefore do not accurately measure free testosterone.[8,9] In contrast, direct measurements of bioavailable or free testosterone, using ammonium sulfate precipitation or equilibrium dialysis methods, respectively, or calculated from total testosterone and SHBG measurements, are not affected by alterations in SHBG. Therefore, they provide a more accurate and reliable assessment of biologically active testosterone in blood and are recommended for diagnosis of hypogonadism in the aging male, in whom SHBG levels are higher than in young men. These more accurate testosterone measurements are also preferred, regardless of age, in clinical states where SHBG concentrations are decreased (eg, moderate obesity, nephrotic syndrome, malnutrition, hypothyroidism, glucocorticoid or androgen use) or increased (eg, hepatic cirrhosis, hyperthyroidism, estrogen or anticonvulsant use).[5]

Age-Related Decline in Both Testis and Hypothalamic Function

The age-related decline in serum testosterone levels is due both to diminished testis production of testosterone and to reduced hypothalamic secretion of gonadotropin-releasing hormone (GnRH), resulting in inadequate luteinizing hormone (LH) secretion by the pituitary gland.

The number of Leydig cells, amount of basal testosterone production, and testosterone secretion in response to stimulation by LH or human chorionic gonadotropin (hCG) administration decline significantly as men age.[4] The metabolic clearance rate of testosterone also decreases with aging, lessening the impact of reduced testosterone production on circulating testosterone concentrations. The circadian variation in serum testosterone levels, with peak concentrations in the morning, is blunted in healthy older men compared with young men, suggesting an alteration in hypothalamic circadian pacemaker function.[10] Although early morning serum testosterone concentrations are lower in older men compared with young men, late afternoon values are not significantly different. Therefore, in evaluating hypogonadism in aging men, serum testosterone levels should be assessed in morning (8:00 AM) blood samples.

The age-related decline in serum testosterone levels is accompanied by a gradual increase in serum gonadotropin, follicle-stimulating hormone (FSH), and to a lesser extent LH concentrations.[1,3] Although pituitary gonadotropin levels increase with aging, they usually remain within the wide normal range for young men. The resulting hormonal pattern of low serum testosterone and normal gonadotropin levels in older men suggests concomitant age-related secondary hypothalamic–pituitary dysfunction in conjunction with primary testicular failure. Low serum testosterone and normal gonadotropin levels (consistent with secondary hypogonadism) is the most common hormonal pattern found during the work-up of hypogonadism in the aging male.

Table 1
Age-Related Physiological Changes Consistent with Androgen Deficiency

Body Composition	Brain Function
↓ Lean body mass	↓ Libido and erections
↑ Fat mass	↓ Energy
↓ Muscle mass and strength	Irritability and depressed mood
↓ Bone mineral density	↓ Cognitive function
↓ Male hair and skin thickness	↓ Sleep quality

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Frequent blood sampling studies to assess the pulse characteristics of LH levels provide indirect evidence for age-related alterations in pulsatile hypothalamic GnRH secretion and stimulation of the pituitary gland. Compared with testosterone-deficient young men, healthy older men with low serum testosterone levels demonstrate a relatively slow LH pulse frequency, reduced LH pulse amplitude, and more chaotic LH secretion, suggesting an impairment of the hypothalamic GnRH pulse generator with aging.[11–13] Furthermore, the pulsatile LH response to reduction of testosterone negative feedback induced by administration of an androgen receptor antagonist, flutamide, or androgen synthesis inhibitor, ketoconazole, is attenuated in older compared with young men.[14,15] In contrast, LH secretion in response to chronic pulsatile GnRH administration is similar in older and young men, suggesting that given adequate GnRH stimulation, pituitary gonadotropin production is unaffected by aging.[16]

Optimal clinical management of age-related alterations in physiological function requires careful attention to all potential etiological factors.

Changes in Androgen Action and Active Metabolism of Testosterone with Aging

A systematic evaluation of age-related changes in androgen action in target tissues has not been performed. Androgen receptor (AR) gene expression in some areas of the brain (eg, hippocampus) and the number of androgen binding sites in genital skin are decreased in older compared with young men.[4] In older men without benign prostatic hyperplasia (BPH), AR expression and nuclear AR content in the prostate are similar to those of young men.[4] However, AR expression is reduced, and total and nuclear AR levels are increased in older men with BPH compared with young men.

The trinucleotide CAG repeat length within the first exon of the AR gene is highly variable and associated with variations in AR transcriptional activity. A shorter CAG repeat length is associated with greater AR transcriptional activity and possibly greater androgen action.[17] Interestingly, age-related changes in serum total and free testosterone levels are associated with the CAG repeat length within the AR gene.[18] Older men with lower serum testosterone concentrations have a shorter CAG repeat length and possibly greater androgen activity. A shorter CAG repeat length is also associated with an increased risk for and severity of BPH and prostate cancer.[19,20]

Androgen action is mediated by binding of androgen ligands such as testosterone to the AR, and interaction of this complex with tissue-specific co-activators and co-repressors on androgen-response elements of specific genes in target tissues to modulate transcription.[21] Age-related alterations of these co-regulators and other transcription factors in androgen target tissues, and the effects of these changes on androgen action have not been investigated. However, in

addition to declining serum testosterone levels, alterations in androgen action may also play important roles in the age-related alterations of physiological function and the pathophysiology of age-related pathologies, such as prostate cancer.

Testosterone is actively metabolized to the estrogen, estradiol (E_2) and 5 α-dihydrotestosterone (DHT), a more potent androgen than testosterone, by the enzymes aromatase and 5 α-reductase type 1 and 2, respectively.[5] Many testosterone actions are mediated, at least in part, by its active metabolites, E_2 (eg, on bone, brain, and lipids) and DHT (eg, on prostate). Despite declining serum testosterone levels, total E_2 and DHT concentrations do not change (or else decrease only slightly) with aging, suggesting a relative increase in conversion of testosterone to E_2 and DHT, and/or reduction in the metabolic clearance of these active metabolites.[1,22] Because SHBG concentrations increase, serum bioavailable or free E_2 and DHT levels decline with aging. The physiological significance of bioavailable E_2 and DHT is not clear; however, recent studies suggest that the age-related decrease in bioavailable E_2 levels correlates better than total or bioavailable testosterone with the decline in bone mineral density in men.[23] Tissue DHT levels decrease in the epithelium, and E_2 levels increase in the stroma of normal and BPH prostate glands with aging, emphasizing the importance of considering active metabolism of testosterone within specific regions of androgen target organs.[24]

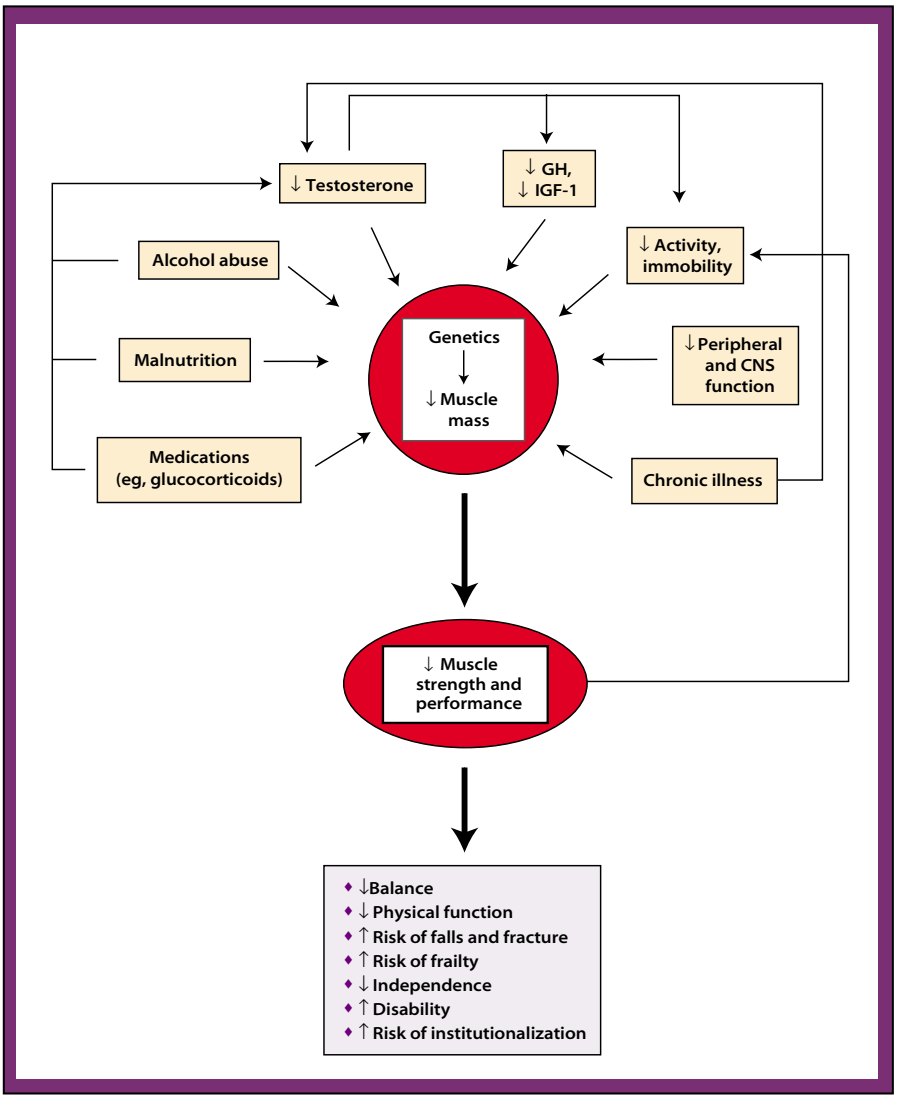

Figure 3. *Schematic diagram of the multiple factors that may contribute to decreased muscle mass, resulting in reduced muscle strength and performance in older men. These factors include: low free or bioavailable testosterone levels; low growth hormone (GH) and insulin-like growth factor 1 (IGF-1) concentrations; lifestyle (eg, alcohol abuse); malnutrition; use of medications that reduce muscle mass (eg, glucocorticoids); decreased activity or exercise, or immobility; peripheral and central nervous system (CNS) dysfunction; chronic illnesses that reduce muscle mass; and genetic factors that influence muscle metabolism. The decline in serum testosterone levels may contribute to the decrease in GH and IGF-1 levels and to reduced activity (as a result of weakness and/or poor motivation). Furthermore, alcohol abuse, malnutrition, certain medications (eg, glucocorticoids) and chronic illnesses may decrease serum testosterone levels further. Reduced muscle strength and performance may predispose to decreased balance; reduced physical function; increased risk of falls and fractures; and an increased risk of frailty that is associated with loss of independence, increased disability, and increased risk of institutionalization.*

Age-Associated Physiological Changes Consistent with Androgen Deficiency

A number of physiological alterations, many of which are known to be regulated by androgens, occur concurrently with the age-related decline in serum testosterone levels. These aging-related physiological changes include decreased lean body mass and increased fat mass; reduced muscle mass and strength that contribute to decline in physical function; decreased bone mineral density that contributes to increased risk of fractures; decreased body hair and skin thickness; diminished sexual function (reduced libido and sexual activity, and erectile dysfunction); reduced energy, vigor, and general well-being; irritability and depressed

mood; impaired cognitive function; and impaired sleep quality (Table 1).[4]

Similar alterations in physiological function occur in androgen-deficient young hypogonadal men, and testosterone replacement therapy improves these functions. Therefore, it is postulated that the decline in serum testosterone levels with aging contributes, at least in part, to these age-related alterations in physiological function, especially in older men whose serum testosterone levels are consistently below the normal range for young men. Although not found uniformly, most descriptive studies have found a correlation, albeit weak, between serum testosterone levels and most of these physiological functions, independent of age.[4] Given the multifactorial nature of age-related alterations in physiological function (see below), it is not surprising that the correlation between serum testosterone levels and the physiological changes that occur with aging cannot be solely attributed to testosterone.

Multifactorial Etiology of Age-Related Physiological Changes

The etiology of most age-related alterations in physiological function is multifactorial. As with low testosterone, some of the factors contributing to functional decline with aging are modifiable or treatable, and optimal clinical management requires careful attention to all potential etiological factors. For example, in addition to low testosterone levels, important contributors to the age-related decrease in muscle mass (sarcopenia) resulting in reduced muscle strength and performance include low growth hormone (GH) and insulin-like growth factor-1 (IGF-1) concentrations; lifestyle (eg, excessive alcohol intake); poor nutrition; use of certain medications (eg, glucocorticoids); lack of exercise or inactivity due to weakness or immobilization; peripheral and central nervous system dysfunction; chronic illnesses; and a predisposing genetic background (Figure 3).

Interactions among the potential causal factors that contribute to age-related physiological decline increase the clinical complexity and highlight the importance of using a multifactorial approach when managing older patients. For example, low serum testosterone levels may contribute to reductions in GH and IGF-1 concentrations and inactivity or lack of exercise (as a result of weakness and/or poor motivation). Also, many of the factors that decrease muscle mass (eg, malnutrition, medications, excessive alcohol intake, and chronic illnesses) may contribute to the reduction in serum testosterone levels with aging. Correction of poor nutrition, discontinuation of certain medications (eg, glucocorticoids), and abstinence from alcohol may increase serum testosterone concentrations and circumvent the need for testosterone treatment.

Aging-associated physiological changes have important potential clinical consequences. For example, reduced muscle strength and performance may impair balance and physical function; increase the risk of falls and fractures; and increase the susceptibility to frailty which is associated with loss of independence, disability, and increased need for assisted living or long-term care (Figure 3).

Clinical Trials of Testosterone Therapy in Older Men

The physiological and potential clinical significance of the age-related decline in serum testosterone concentrations has been assessed initially in limited clinical trials of testosterone therapy in older men. To date, relatively few randomized controlled studies of up to 3 years' duration have been performed. These studies have used a variety of testosterone formulations to treat small numbers of mostly healthy older men with serum testosterone levels slightly below or in the lower part of the normal range for young men, and different methods were used to assess outcomes. However, these initial controlled studies suggest that testosterone treatment in older men may have beneficial effects on body composition (increased lean body mass and decreased fat mass), bone mineral density, and possibly on muscle strength, sexual function, general well-being, aspects of cognitive function, low-density lipoprotein cholesterol, angina, and exercise-induced cardiac ischemia.[4,25] However, these studies have not been powered sufficiently to evaluate the long-term beneficial effects of testosterone treatment in older males with hypogonadism on clinical outcomes, such as reduction in the incidence of fractures, diabetes mellitus, myocardial infarction, stroke, coronary death, depression, or dementia.

In these initial controlled clinical studies, testosterone therapy in older men has been tolerated very well. The only adverse effect that has been found consistently in some men is stimulation of excessive erythrocytosis.[4,25] Some studies have also found a small but statistically significant increase in prostate-specific antigen levels within the normal range (ie, <4 ng/mL).[4,25] However, as with potential beneficial effects (see above), a major caveat of the controlled studies performed so far is that they have been powered insufficiently to evaluate the long-term risks of testosterone therapy, in particular on clinical prostate and cardiovascular disease.

Summary and Conclusions

Serum testosterone levels decline

gradually and progressively with aging in men, and the proportion of men with circulating testosterone concentrations below the normal range for young men increases with age. Because serum SHBG levels increase with aging, serum free and bioavailable testosterone levels decline at a more rapid rate than total testosterone concentrations. This age-related decrease in testosterone levels is due both to primary testicular and secondary hypothalamic GnRH dysfunction, and is accentuated by concomitant co-morbid illnesses, use of certain medications, and malnutrition. Aging-associated alterations in body composition, decreased energy and muscle strength, reduced sexual function, changes in mood, and diminished cognitive function occur in conjunction with declining serum testosterone levels. Similar alterations occur in young androgen-deficient hypogonadal men and are improved with testosterone replacement therapy. Therefore, it is postulated that age-related androgen deficiency may contribute, at least in part, to the changes in physiological function that occur with aging.

The potential physiological and clinical significance of low serum testosterone levels in older men is supported by descriptive studies that find a correlation between testosterone levels and these physiological functions, as well as by initial short-term controlled studies of testosterone therapy in small numbers of healthy older men that suggest some beneficial effects (eg, on body composition and bone mineral density) without significant adverse effects, except for excessive erythrocytosis in some men. Given these findings, it is reasonable to consider testosterone replacement therapy for older men who have a clinical syndrome consistent with androgen deficiency and repeatedly low serum free and bioavailable testosterone levels, in whom the potential benefits of therapy may outweigh the potential risks. Because age-related alterations in physiological function are usually a result of multiple etiologies, it is important to evaluate and treat other factors (eg, poor nutrition, confounding illness and medication, inactivity, and excessive alcohol use) in addition to low testosterone levels that may contribute to the clinical manifestations in older hypogonadal men.

A major caveat in treating older men with testosterone is that long-term benefits (eg, on fracture incidence, onset of dementia, major cardiovascular outcomes, physical function, frailty and quality of life, and risks of clinical prostate disease [BPH and prostate cancer] and cardiovascular disease) are not known. The balance of benefits and risks of testosterone therapy in older men with low testosterone levels needs to be determined in carefully designed large, long-term, randomized, placebo-controlled studies. Until the results of these studies are available, practitioners must rely on sound clinical judgment in managing hypogonadism in the aging male. ■

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Main Points

- Decline in testosterone occurs concurrently with a number of age-associated changes in androgen-regulated physiological functions, including alterations in body composition, decreased energy and muscle strength, reduced sexual desire and function, changes in well-being and mood, and diminished cognitive function.
- *Hypogonadism* in the aging male is most appropriately defined as a decline in serum testosterone to levels below the normal range for young men, with associated clinical manifestations consistent with androgen deficiency.
- The age-related decline in serum testosterone levels is due both to diminished testis production of testosterone and to reduced hypothalamic secretion of gonadotropin-releasing hormone, resulting in inadequate luteinizing hormone secretion by the pituitary gland.
- Initial controlled studies suggest that testosterone treatment in older men may have beneficial effects on body composition, bone mineral density, and possibly on muscle strength, sexual function, general well-being, aspects of cognitive function, low-density lipoprotein cholesterol, angina, and exercise-induced cardiac ischemia. However, the long-term benefits and risks of testosterone administration in older men are not known.
- Because age-related alterations in physiological function are usually a result of multiple etiologies, it is important to evaluate and treat other factors (eg, poor nutrition, confounding illness and medication, inactivity, and excessive alcohol use) in addition to low testosterone levels that may contribute to the clinical manifestations in older hypogonadal men.

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